DSMBs-Introduction

Janet Wittes, PhD
Statistics Collaborative
Washington DC

Five grim fairy tales

1. Sharing data (Rezulin)
2. FDA interaction (ACTION I and II)
3. Lousy communication (post-MI)
4. Inexperienced DSMB (post-CABG)
5. Failure to specify goals (sepsis)

Outline

- Structure
- Regulatory considerations
- Reporting
- Monitoring safety
- Monitoring efficacy
- Conclusion

Themes

- Good tools for good decision-making
- DSMB's role must be clear
- Communication is complex
- Each DSMB has its unique sociology
- Necessity of trust

All studies need safety monitoring

- But not all need a DSMB
- DSMBs are:
  - Expensive
  - Time consuming
  - Cumbersome
- May not be needed for behavioral trials

Problems knowing interim results

- Scientific – relevant to behavioral trials
- Not relevant
  - Regulatory
  - Financial: SEC

Changes over time

- Medicine, science, & financial circumstances change…
- leading to desire to change an ongoing clinical trial
  - primary endpoint
  - entry criteria, evaluable population
  - concomitant medications
  - size of the trial
- Or plan a new trial (or, for products, build factory)
- Not OK if change proposed knowing interim results

Therefore, a DSMB…

- A committee charged with monitoring
  - safety
  - efficacy
  - progress of a clinical trial
- May advise about
  - change in protocol
  - change in procedure

Rationale for DSMB

- Ethical compact protecting participants in trials
- Sponsor
  - regulations for reporting during trial
  - financial incentive to end trial early
    - ✓ If intervention has no effect
    - ✓ If intervention is a smashing success

What trials need a DSMB?

- Rule of thumb: a trial for which the combination of investigator, sponsor, IRB, and regulatory bodies is insufficient to monitor safety
  - Multicenter
  - New chemical entity
  - Hard clinical endpoints
  - Vulnerable population
- Or, trial with interim analyses for efficacy

What trials don't need a DSMB?

- Phase I?
- Unblinded?
- Very short trials
- Well-studied drug or class?
- Behavioral study in nonvulnerable pop?

Function of DSMB defines roles and structure

- Three roles
  - Scientific/operational integrity
  - Safety
  - Efficacy
- Size & composition
- Specific concerns direct analysis and reports
  - Safety
  - Efficacy

Responsibilities

- Interim monitoring of trial information
  - Unblinded efficacy and safetu data
  - Measures of study conduct
    - ✓ accrual
    - ✓ compliance
    - ✓ completeness and speed of data collection
- Review information from external studies

Membership

- Independent and disinterested both financially and intellectually
  - Not an investigator
  - Limited (?) other relationship with sponsor
- 3 to 10 people covering relevant fields
- Experienced chair and statistician
  - Or: Reporting Statistician experienced enough to train DSMB statistician

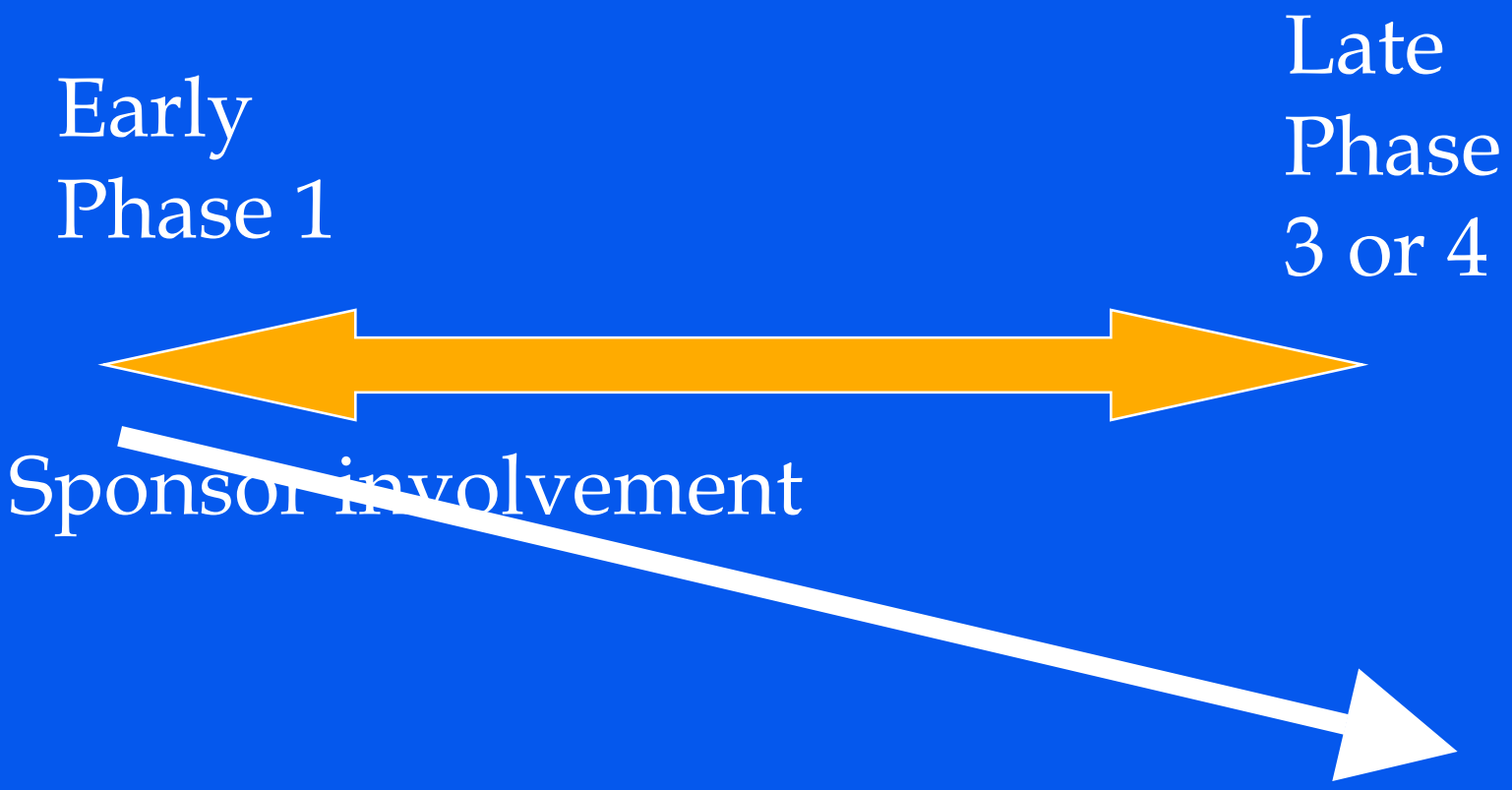
Composition of DSMB

- Clinicians with relevant expertise
  - behavioral
  - clinical
  - cultural
- Statistician expert in clinical trials
- Ethicist (?)
- Epidemiologist (?)

Structure of DSMBs

- Not independent, solely by sponsor
- Independent members + sponsor
- Voting members all independent; sponsor present
- Voting members all independent; a statistician the sponsor pays who presents the data also present
- All attendees independent
- Etc.

Recommendation



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ICH Guidance E6

- Sponsor may use an IDMC to assess the progress o
  a clinical trial (safety and efficacy)
- Recommend to the sponsor whether to
  - continue
  - modify
  - stop a trial
- IDMC needs written operating procedures (E9)
- Must maintain written records of all meetings (E9)

ICH E9 Statistical Guidance: IDMC responsibilities

- Independence necessary to:
  - Control sharing of important comparative information
  - Protect integrity of the trial from adverse impact of access to trial information

ICH E9: planning

- "Because the number, methods and consequences of these comparisons affect the interpretation of the trial, all interim analyses should be carefully planned in advance and described in the protocol."

ICH E9: IDMC Procedures

- …Sponsor representatives on the IDMC should be clearly defined in the operating procedures (e.g., voting)
- ... the procedures should address the control of dissemination of interim trial results within the sponsor organization

Goals of interim analysis (ICH E9, *4.5*)

- To stop the trial early if:
  - superiority of treatment is clearly established
  - the demonstration of a relevant treatment difference has become unlikely (futility)
  - unacceptable adverse effects are apparent

United States:
Guidance for Clinical Trial Sponsors

On the Establishment and Operation of Clinical Trial Data Monitoring Committees

http://www.fda.gov/cber/gdlns/clindatmon.pdf

Purpose of the Guidance

"…to assist sponsors of clinical trials in determining when a DMC is needed for optimal study monitoring, and how such committees should operate."

Definition of DMC

A DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical trial.

The DMC advises the sponsor regarding the continuing **safety** of current participants and those yet to be recruited, as well as the **continuing validity** and **scientific merit** of the trial.

Sponsor

- Body required under the law to monitor studies evaluating new drugs, biologics, and devices
- Delegates of the sponsor
  - Steering Committee
  - Contract Research Organization

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To whom does the DSMB report?

- The holder of the NDA?
- The funder?
- The Steering Committee?
- Regulatory bodies?
- The IRBs and ERCs?

Change in protocol

- Answer questions posed by designers
- Suggestions in response to surprising observation

Schedule and structure of meetings

- Protocol or charter defines meeting frequency and interim analysis plans
- Well-defined charter
- Face-to-face meetings preferred
- Open session - to interact with sponsor, investigators, etc.
- Closed session - to review unblinded data
- Executive session

Access to data

- Until the blind is broken-only DSMB
- Requests will come from:
  - IRBs/ERBs
  - European regulatory bodies if a drug arm
  - Investigators
  - Sponsor if a drug arm

Early termination or protocol modification

- DSMB recommendation are advisory
- Sponsor should report back to DSMB

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Monitoring safety

- Searching for the unknown
- Rare events; unexpected
- Major problem of multiplicity

Who monitors safety?

- Investigator: direct responsibility to participant
- Sponsor: regulatory responsibility for safety
- IRBs/ERBs: continuing safety of protocol
- Regulatory bodies: receives reports from trial and related products – if drug
- DSMB-sees unblinded data for entire study

What type of safety bounds?

- None-just DSMB judgment
- Futility bounds for efficacy provide safety bounds
- Symmetric- as hard to declare something unsafe as to declare efficacy
- Asymmetric bounds – cut-off for safety less stringent than for efficacy
  - we don't need to *prove* harm

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Monitoring efficacy

- Statistical issues "solved"
- Boundaries for monitoring efficacy require unequivocal evidence in order to stop early

Sample size

- If we have 90 percent power at end of study, what would our power be earlier?
- N/4 40%
- N/2 60%
- 3N/4 80%

Why can't you look over and over?

- In the long run, everyone is dead.-Keynes
- # of tests — Overall Type I error rate

# of tests	Overall Type I error rate	
1		=0.05
2	$1-(1-.05)^2$	=0.08
10	$1-(1-.05)^{10}$	=0.19
100	$1-(1-.05)^{100}$	=0.37
Infinity	$1-(1-.05)^{\infty}$	=1

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Time Course

- Meets infrequently
  - Semi-annually
  - Every ¼ of endpoints
- May review safety more frequently
- Meetings change over time
  - Early: decide what to see
  - Middle: monitor with view to decisions
  - End: recommendations for publication

Don’t overuse DSMBs

- A DSMB is
  - Time consuming
  - Expensive
  - Administratively complex
- Think hard before you set one up
  - Make sure it has a clear purpose
  - And everyone knows what it is